CHAPTER

9

Effects of Psychological Stress on Telomeres as Genome Regulators

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OUTLINE

KEY POINTS

- Telomeres are protective nucleoprotein caps at the ends of chromosomes that can shorten with chronological age and environmental exposures.
- Evidence exists for a relationship between psychological stress and telomere shortening.
- The proximal mechanisms of telomere shortening due to psychological stress may be different during fetal development, childhood, and adulthood and may include epigenetic programming of stress reactivity systems, changes in levels of systemic inflammation, and increased oxidative stress.
- Progressive shortening of telomeres may give rise to stepwise changes in gene expression through alterations in telomere dynamics via the telomere position effect (TPE), levels of TERRA, and association of shelterin proteins.
- Future work in the field of stress biology may benefit by expanding the understanding of the function of telomeres to include genome regulation.

INTRODUCTION

Telomeres are capping structures that protect the ends of linear chromosomes against damage as part of a system regulating cell longevity and aging. Humans have 92 telomeres per cell, with one telomere capping each end of 46 linear chromosomes (i.e., 23 chromosome pairs). Telomere shortening in dividing cells over the life span occurs due to the inability of cells to fully replicate DNA ends during division. Cells having reached the maximum number of divisions possible before losing critical nontelomeric DNA will either enter a nondividing survival state (cellular senescence) or undergo programmed cell death (apoptosis). Though not yet verified longitudinally, cross-sectional evidence in humans suggests a nonlinear decline in the average telomere length after birth with a significant drop in the first years of life followed by relatively stable decline until death.[1] At birth, telomere length is influenced by factors including sex, race/ethnicity, the father's age at conception, and maternal inheritance. Genetic variation accounts for approximately 70% of interindividual differences in telomere length.[2]

Additionally, environmental factors such as diet, physical activity, smoking, obesity, psychological disorders, stress, socioeconomic status, and other external exposures have been shown to influence telomere length.[3]

Research on telomeres and exposures has mainly utilized a measure of telomere length averaged across all chromosomes in all cells in a sample. Given that a single critically short telomere can be the limiting factor in a cell's replicative capacity, averaging across many telomeres may obscure the true effect of environmental exposures on telomeres. The role of critically short telomere length will be discussed in this chapter, nonetheless averaged shorter telomere length has been linked to increased all-cause mortality and cardiovascular disease risk,[4] while averaged longer telomere length has been linked to increased risk for certain cancers.[5]

In addition to the role of short telomeres as a trigger for genomic instability and changes in cellular phenotype, further evidence exists that the structural dynamics of telomeres, as influenced by their length may be an important factor in maintaining genomic stability.[6] Progressively shortening telomeres may give rise to stepwise changes in gene expression that alter cellular state.[7] In other words, aging and disease-related cellular changes may be driven by structural alterations in telomeres long before a critically short telomere length is reached. This hypothesis is pertinent to the observed relationship among telomere length, psychological stress, and aging and disease; the modest telomere shortening associated with psychological stress may be of greater physiological importance than previously assumed.

This review aims to summarize evidence for and mechanisms of telomere shortening due to psychological stress over the life span, with a discussion of telomeres as genome regulators. It is meant to be an introductory reading rather than a comprehensive analysis of the topic. In the following, we discuss how the structure of telomeres, as influenced by their length, works to regulate gene expression in the context of psychological stress. After a brief overview of basic telomere structure, we summarize evidence for the relationship between psychological stress and telomere shortening over the life span. We discuss current understanding of the mechanisms by which psychological stress impacts telomeres. We then present evidence for telomere regulation of gene expression via progressive telomere shortening followed by the consequences of critically short telomeres on cellular phenotype. In closing, we discuss implications of this work and point to future directions for the field.

TELOMERE LENGTH AND STRUCTURE

Telomeres are structures capping the ends of DNA composed of repetitive sequences of nucleotides (5′-TTAGGG-3′ in vertebrates). For humans, each chromosome is protected by several kilobase pairs of telomeric repeats, though this number is known to vary with internal and external regulatory factors.[3] Each telomere has a double-stranded region ending with a single-stranded overhang. These regions fold into a telomeric loop structure that is regulated and protected by shelterin proteins (TRF1, TRF2, POT1, RAP1, TIN2, and TPP1).[8] Telomeres, in turn, protect the ends of linear chromosomes from damage in much the same way that plastic caps protect the ends of shoelaces.

Though long considered transcriptionally silent, it is now known that telomeres are transcribed into variable-length noncoding RNA sequences called telomeric repeat-containing RNA (TERRA). TERRA associates with telomeres in a cell cycle- and telomere length-dependent manner.[9] Telomeric repeats, shelterin proteins, and TERRA condense into structures called nucleosomes by coiling tightly around associated proteins, like string coiling around a yo-yo. These regions of tightly packed DNA are then further compacted and organized within the nucleus of each cell.[10]

Critically short telomeres in vitro can trigger cellular senescence and apoptosis. In vivo short telomeres are associated with chronological age, age-related disease risk, and mortality.[8] In stem cells and transiently in certain immune cells, telomeres can be elongated by telomerase, an enzyme that copies an associated RNA template into new telomeric DNA. After birth the action of telomerase is not enough to counteract telomere shortening occurring with cell division; thus telomeres in stem cells also shorten with age.[11]

The age-dependent shortening of telomeres, coupled with the shortening observed cross sectionally due to environmental stressors, has given rise to the view of telomeres as cellular "clocks" that can be used to distinguish biological age from chronological age.[12] Telomere length, functioning as an indicator of cellular aging, may then represent a useful metric to quantify the impact psychological stress has at the cellular level. In the following section, we give an overview of the evidence for a relationship between psychological stress and telomere length over the life span before discussing possible mechanisms for such a relationship.

PSYCHOLOGICAL STRESS AND TELOMERES

Telomere Shortening in Response to Psychological Stress Across the Life Span

Psychological stress has been associated with shorter telomere length across the life span; however, evidence suggests that the prenatal period is a particularly

sensitive developmental time. Exposures sustained prenatally can affect multiple characteristics of an individual's biology for the remainder of the life span.[13] Prenatal exposure to maternal psychological stress is associated with shorter telomeres at birth[14] and in later life.[13] Suboptimal pregnancy conditions, including high maternal psychological stress, have also been linked to dysregulated telomerase activity.[13] This has implications for telomere regulation throughout the rest of the life span; less active telomerase in stem cell pools may result in faster rates of telomere shortening.

Childhood represents an additional developmentally sensitive period, with exposures incurred during this time having measurable impact throughout the remainder of life. Though many of these findings have been drawn from cross-sectional data, childhood exposure to adversity and psychological stress is associated with shorter telomeres during childhood[15] and in later life.[16] Rapid telomere shortening in early life due to somatic growth may be exacerbated by traumatic experiences. Shalev et al. (2013) demonstrated greater longitudinal shortening in telomeres for children with two or more forms of violence exposure than for matched individuals not exposed.[17] Similarly, children exposed to institutional care had faster rates of telomere shortening in a dose–response manner than those not exposed to institutional care when measured longitudinally at ages 2–4[18] and 6–8.[19]

Adult exposure to psychological stress has also been associated with shorter telomeres, though interindividual differences in adulthood seem to be mainly driven by length setting processes during prenatal and early childhood development. Metaanalyses indicate that adults reporting chronic exposure to perceived psychologically stressful events, including poverty, caregiving, and violence, have shorter telomeres on average than matched adults without chronic stress.[20] These associations tend to be weaker for individuals reporting stress exposure only in adulthood and stronger for those reporting stress exposures either during childhood or during both childhood and adulthood. The stronger association for childhood stress exposure and adult telomere length points to the likely developmental sensitivity of the telomere system preadulthood.[12] Studies of psychological stress and telomere length at each stage of the life span tend to be cross-sectional and reliant on convenience samples. To validate these findings, longitudinal studies with prospective assessment of psychological stress and repeated telomere length measurements are needed.

Mechanisms Linking Psychological Stress and Telomeres

In addition to longitudinal studies, research is needed to elucidate the mechanisms by which psychological stress interacts with the telomere system. Existing research in this area has focused on inflammation and oxidative stress.[14] Epigenetic programming during prenatal and childhood periods has also been implied as a mechanism by which early life stress continues to influence telomere dynamics throughout life. Epigenetic programming refers to the influence of nongenetic factors on gene function. During developmentally sensitive periods, DNA can interact with environmental cues to alter gene function (e.g., which genes will be activated or silenced) in such a way that an individual will be maximally fit for their predicted future environment.[21] This programming can result in an individual being chronically over- or underreactive to future environmental cues. While research emphasis has been given to the role of inflammation, oxidative stress, and epigenetic programming in the relationship between psychological stress and telomeres, the exact mechanisms will likely vary across developmental periods, necessitating a developmentally sensitive approach to future research in this area. In the succeeding text, we summarize current understanding of the mechanisms linking psychological stress and telomeres at three developmental stages.

Specifically during prenatal development, maternal psychological stress can be transferred to the intrauterine environment through higher levels of circulating maternal cortisol and catecholamines.[13] These stress hormones have been implicated in the initial setting of fetal telomere dynamics via induced oxidative stress and interference with the fetal telomerase activity.[13] Exposure to increased levels of cortisol may program the fetal hypothalamic–pituitary–adrenal (HPA) axis, likely through epigenetic modifications, thus influencing stress reactivity tendencies for the remainder of life.[22] Increased maternal psychological stress has been further linked to decreased rate of uterine blood flow, which can lead to a low oxygen environment that induces oxidative stress in the fetus.[13]

Programming of telomere length at birth and of the HPA axis prenatally and during childhood has implications for future neuroendocrine stress reactivity and telomere dynamics. Though there is evidence for resilience, some individuals exposed to the intrauterine environment of a stressed mother may be born with shorter telomeres, increasing their likelihood of developing diseases of aging prematurely.[13] Further, exposure to adversity during childhood may also dysregulate the HPA axis and future stress response, providing a mechanism by which the impact of childhood stress on telomere length persists into adulthood.[21] Additionally, new research has extended the recognized window of epigenetic programming of the HPA axis throughout adulthood, indicating the possibility of some measure of flexibility in stress reactivity systems throughout the life span.[23]

While programming of neuroendocrine systems may be a proximal result of adversity suffered, the direct mechanism of impact psychological stress has on

telomeres is currently thought to be mediated through inflammatory cytokines and increased oxidative stress.[15] Experiencing psychologically stressful events has been shown to increase levels of circulating inflammatory cytokines.[24] Several of these inflammatory signals work to activate the HPA axis and promote release of cortisol, a hormone which in turn terminates the inflammatory cascade. However, chronic stress exposure may push an individual into a proinflammatory state wherein the level of inflammation is not fully resolved by the body's antiinflammatory mechanisms.[25] Sustained HPA axis activation due to unresolved inflammation may alter the response of tissues throughout the body to the antiinflammatory effects of cortisol, rendering cortisol less effective in terminating future inflammation. In other words, chronic psychological stress may habituate the body to cortisol, facilitating the development of chronic inflammation.

Exposure to chronic inflammation is linked to increased production of reactive oxygen species,[25] increasing intracellular oxidative stress and subsequent cellular damage. Oxidative stress occurs when levels of oxidants, mainly reactive oxygen species generated endogenously by mitochondrial function or supplied exogenously, rise above the antioxidant capacity of the cell. The G-rich nucleotide sequences of telomeres (e.g., TTAGGG) are particularly prone to oxidative damage, which is difficult to repair due to the blocking of DNA damage repair systems by the shelterin complex surrounding telomeres.[26] The cumulative damage incurred through oxidative stress interferes with cellular function can lead to cellular senescence or apoptosis.[26] Supporting this theory, exposure to psychological stress is associated with both increased cellular oxidative damage[27] and shorter telomeres.[28] While the aforementioned mechanisms have been implicated in stress-induced telomere regulation, in the next section, we discuss the impact of psychological stress on telomeres as genome regulators.

TELOMERES AS GENOME REGULATORS

Evidence for the Function of Telomeres as Genome Regulators

The length of individual telomeres has functional significance to aspects of gene transcription, genome-wide chromatin structure (how tightly compacted the genome is within the nucleus), cellular metabolism, and cell fate.[29] Cellular-level changes have physiological consequences for tissue function, which can manifest as organism-level aging and disease phenotypes. The dominant research focus has been on the "length threshold effect" or the idea that notable changes, such as initiation of the DNA damage response and triggering of apoptosis or senescence, occur when critically short telomere length is reached. For instance, critically short telomeres leading to tissue dysfunction has been implicated in diseases marked by early onset of aging phenotypes, such as progeria syndromes.[30] Despite the focus on critically short telomeres, changes in gene expression with progressive shortening of telomeres have been observed.[31] This has implications for the significance of psychological stress on functional outcomes; the influence of telomeres on aging and disease may be a series of steps rather than a sudden triggering of changes when a critically short telomere length is reached. For progress to be made in quantifying the impact of progressive shortening on cellular phenotype, the issues of telomere measurement must be addressed. Presently, methodological inconsistencies in quantifying telomere dynamics are masking the ability to detect small, gradual changes in vivo; thus much of the discussion on telomeres and gene expression regulation below relies on research conducted in animal models and in cultured human cells. The influence of telomeres on gene expression has been demonstrated in yeast, mouse models, and cultured human cells with a consistency of results that points to evolutionarily conserved mechanisms.

In the following, we discuss how telomeres influence expression of genes throughout the genome via (1) direct interactions with genomic regions outside of telomeres (e.g., telomere position effect), (2) generation of telomere length- and cell cycle-dependent levels of TERRA, and (3) acting as a sequestration site for telomere associated proteins.

Telomere Position Effect

Telomeres form loop structures encompassing telomeric and subtelomeric regions. These looping structures bring telomeres near nontelomeric regions of chromosomes, which have been shown to modify expression of genes in these areas. This process is known as the telomere position effect (TPE) for interactions with genes proximal to telomeres or the telomere position effect over long distances (TPE-OLD) for interactions between telomeres and regions up to 10 megabase pairs away (Fig. 9.1).[31] The mechanism of gene expression modification may be through physical blocking of transcription, such as in the observed silencing of genes at subtelomeric regions. Interactions between telomere–chromatin loop structures and genes controlling the activation of telomerase, for example, have been shown to repress transcription, thus preventing activation of telomerase and unwanted elongation of sufficiently long telomeres.[32]

Recent research indicates that the interaction between long telomeres and nontelomeric sites within the genome is not random; the differential expression of genes due to

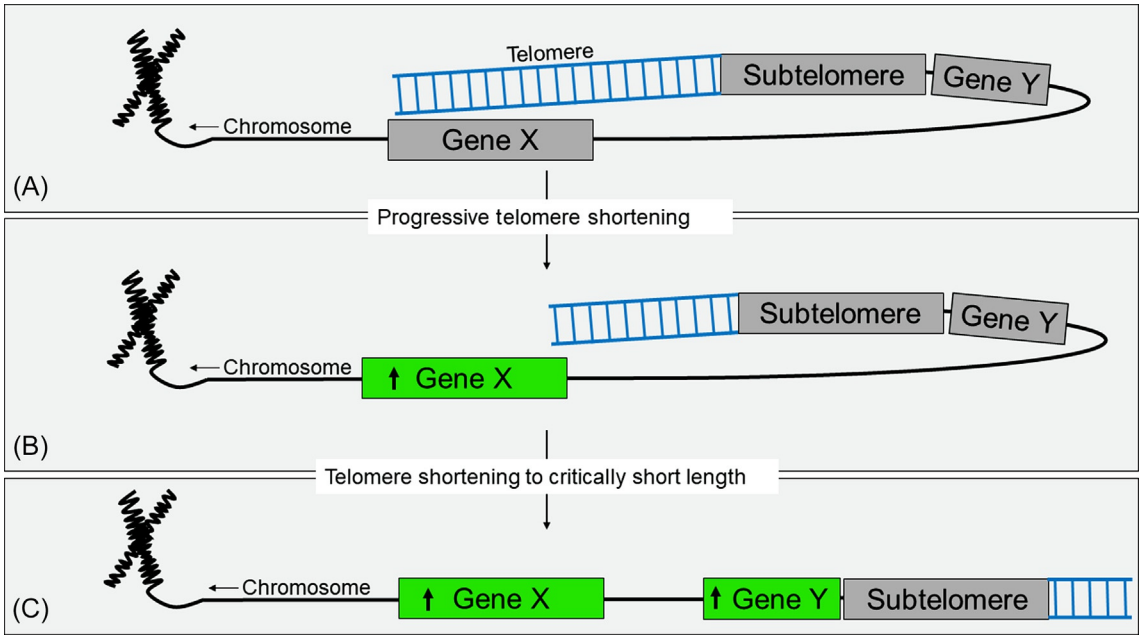

FIGURE 9.1 Telomere position effect (TPE) and telomere position effect over long distances (TPE-OLD). (A) Depiction of TPE-OLD silencing of gene X, possibly via interactions between chromatin loops and regulatory regions of the genome, and classic TPE silencing of gene Y. (B) Hypothesized increase in transcription of gene X with loss of TPE-OLD possibly due to chromatin conformational changes with progressive telomere shortening. (C) Depicted increase in transcription of gene Y with loss of classic TPE at critically short telomere lengths.

short telomeres can be reversed through the elongation of telomeres within the same cell culture.[7] The nucleus contains a highly regulated three-dimensional organization of chromatin that is systematically rearranged by changes in telomere length. The positioning of telomeres within the nucleus and their physical proximity to functional areas of the genome points to the role of TPE in maintaining a stable cellular phenotype.

Telomeric Repeat-Containing RNA (TERRA)

Telomeres, long considered transcriptionally inactive, are now known to produce segments of RNA known as TERRA. TERRA is long noncoding RNA transcribed from subtelomeric and telomeric DNA on each chromosome. TERRA tends to localize to the chromosome from which it was transcribed; however, it can also act in trans at other chromosomes.[33] Levels of TERRA appear to be cell cycle dependent, though the nature of this regulation is unknown. In long telomeres, levels of TERRA are prevented from building up through both epigenetic regulation and destruction of existing transcripts in a cell cycle-dependent manner (Fig. 9.2). Keeping levels of TERRA controlled prevents overproduction of RNA–DNA loop hybrids between TERRA and telomeric DNA.[33] TERRA also competes with transcriptional regulators for binding sites throughout the genome. For instance, binding of TERRA or binding of the RNA helicase ATRX at hundreds of genic sites seems to have opposite functional outcomes, where ATRX binding represses gene expression and TERRA binding increases gene expression.[34] Through this role, TERRA influences the transcription of many genes and assists in stabilizing telomeres. The telomere length-dependent regulation of TERRA levels contributes to a stable cellular phenotype, preventing premature cellular aging, apoptosis, or cellular senescence.[33]

Telomere Associated Proteins (Shelterin Complex)

In addition to the localization of TERRA, shelterin proteins also localize to telomeres by binding to telomeric and subtelomeric regions; however, when nuclear concentrations of these proteins rise, they can bind to other transcriptionally active areas of the genome with functional consequences for gene expression (Fig. 9.3).[35] For instance, RAP1 is recognized as a modulator of the nuclear factor κB (NF-κB)-mediated pathway, which is a pathway involved in controlling cellular inflammatory and immune responses.[35] RAP1 binding at extratelomeric sites has been shown to elicit changes in gene expression related to cell metabolism, adhesion, and apoptosis.[35] Longer telomeres may maintain greater localization of shelterin proteins, decreasing the likelihood of these proteins binding elsewhere in the genome. This localization may delay onset of a cellular aging phenotype.

This work highlights the context in which telomere length as a marker of cellular aging should be placed; telomere length influences telomere dynamics, which in

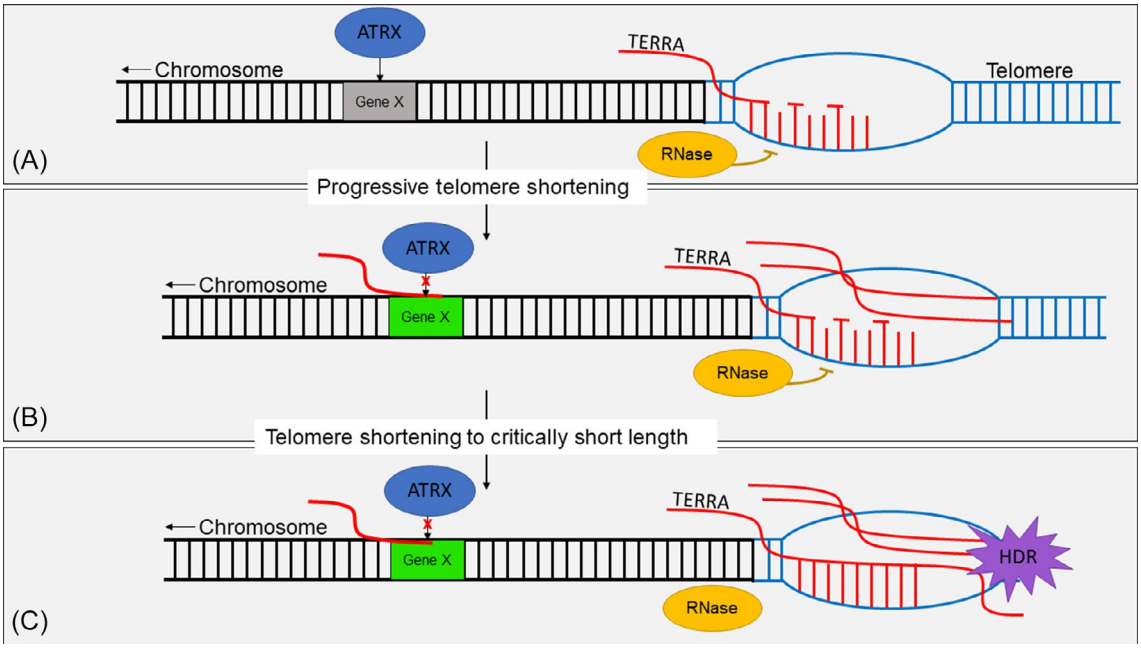

FIGURE 9.2 Changing impact of TERRA at telomeres and throughout the genome with shortening telomere length. (A) Depiction of role of TERRA at long telomeres in assisting the stabilization of telomeres during DNA replication. TERRA is degraded by RNAseH2 and regulated in a cell cycle-dependent manner. (B) Progressive telomere shortening may increase the levels of TERRA produced, possibly changing the availability of TERRA for extratelomeric binding. Throughout the genome, TERRA competes with other binding factors, such as ATRX, for binding at intergenic regions. When TERRA binds instead of ATRX, gene transcription is upregulated. (C) At critically short telomere lengths, TERRA accumulates and forms RNA–DNA hybrid loops with telomeric DNA, interfering with DNA replication and promoting homology-directed repair (HDR) of telomeres.

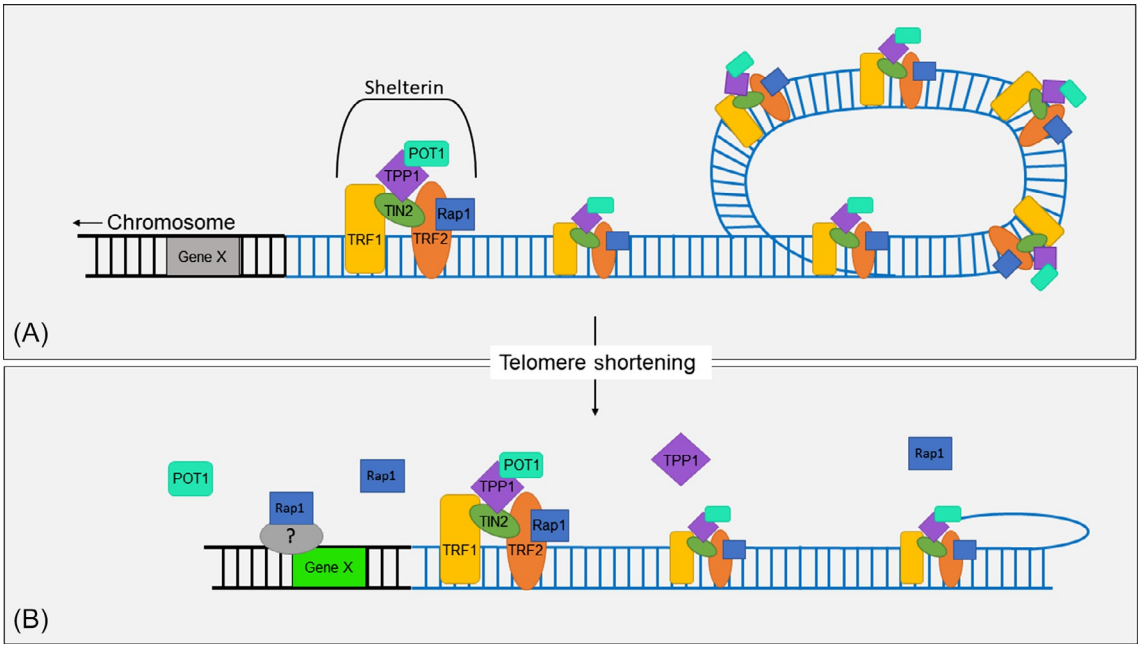

FIGURE 9.3 Telomeres functioning as sequestration sites for shelterin proteins. (A) Depiction of the six-subunit shelterin complex binding to telomeric DNA in the t-loop conformation. TRF1 and TRF2 bind as dimers directly to telomeric DNA, while TIN2, Rap1, TPP1, and POT1 associate in a complex around TRF1 and 2. (B) As telomeres shorten, concentrations of these proteins increase in the nucleus, increasing the likelihood of extratelomeric binding. For example, Rap1 binding (possibly with additional factors) changes transcription of genes associated with cell metabolism, cellular adhesion, and apoptosis.[35]

turn can alter the expression of genes controlling cell fate. In the following section, we discuss the possible functional significance of changes in telomere length due to psychological stress exposure on telomeres as genome regulators.

CONSEQUENCES OF PSYCHOLOGICAL STRESS ON TELOMERES AS GENOME REGULATORS

Telomeres have long been thought of as protectors of the genome, with critically short lengths triggering a sequence of activity attempting to prevent cells with damaged DNA from becoming cancerous. Individuals that have suffered chronic psychological stress have, on average, shorter telomeres than unstressed individuals; however, the effect of psychological stress is small when compared with other internal and external regulators of telomere length, such as genetics or certain health behaviors (e.g., smoking).[3] Here, we present evidence of a role for telomeres of all lengths as genome regulators, capable of inducing changes in gene expression and cellular activity. Through this lens, small changes in telomere length observed with psychological stress may lead to cellular consequences of greater functional significance than previously assumed.

With progressive telomere shortening the expression of genes related to cellular metabolism and stress response is modified,[7, 29] though functional significance has yet to be determined. These changes have been observed in telomeres long before they reach a critically short state. Progressive shortening of telomeres may give rise to altered gene expression due to changes in telomere position effects, levels of TERRA production, and levels of dissociated shelterin proteins.

Reductions in telomere length correspond to increases in levels of TERRA. Through its role in competitive binding with other transcription factors to nontelomeric genic regions, TERRA can modify gene expression throughout the genome.[34] Additionally, TERRA interacts with thousands of proteins, including factors regulating DNA replication and cell cycle progression. Hybrid loops between TERRA and telomeric DNA have been shown to decrease the ability of the cell to replicate telomeric DNA during cell divisions, which may lead to sudden losses of large tracts of telomeric DNA. Thus TERRA likely contributes to nuclear reorganization and transcriptional changes associated with telomere shortening.[33]

Changes in shelterin protein concentrations and binding may represent an additional mechanism of gene regulation by telomeres. Though intracellular proteins are constantly made and destroyed, decreased levels of shelterin proteins at short telomeres are associated with a simultaneous increase in the nuclear concentrations of these same proteins. Rising nuclear concentration of shelterin proteins increases the likelihood of nontelomeric binding and subsequent altering of gene expression.[35] Shelterin protein binding in areas of the genome outside of telomeric and subtelomeric regions has been implicated in regulating expression of genes related to cellular metabolism and immunity.[35] Taken together, increased expression of genes typically suppressed by long telomeres via TPE, as well as modified expression of genes related to cellular metabolism and cell fate by shelterin proteins or TERRA, may give rise to elements of the cellular aging phenotype seen long before telomeres have reached a critically short length.

While it is not yet clear if these changes can be induced by one single critically short telomere in vivo, a large body of research has demonstrated that at critically short lengths, telomeres can induce widespread changes in gene expression and cellular phenotype. Telomere shortening induces 3D restructuring of chromatin as the looping structures of telomeres are destabilized.[36] Critically short telomeres lose the loop structures encompassing telomeric and subtelomeric regions. This modifies transcription of subtelomeric genes that regulate the DNA damage response and cellular fate.[37] Additionally, accumulation of TERRA can trigger apoptosis or cellular senescence through initiation of the DNA damage response, radically altering transcriptional regulation throughout the genome. Destabilization of the 3D telomere structure also decreases association of shelterin, increasing nuclear concentration of these proteins and subsequent binding at nontelomeric sites throughout the genome, altering expression of genes for cellular stress–response, metabolism, and immunity. The changes in cellular phenotype associated with critically short telomeres have been the focus of much research due to their implication in aging and diseases such as cardiovascular disease and several cancers.

FUTURE DIRECTIONS

Functional telomeres maintain stability of the genome, protecting against unwanted DNA damage responses. The structure of long telomeres assists in preventing cells from undergoing apoptosis or entering a state of senescence. As telomeres progressively shorten with successive cell divisions, cells reach their proliferative capacity and are forced into one of these two states. Both are useful processes that protect against aging cells becoming cancerous; however, tissues with many senescent cells develop age-related diseases, and loss of cells due to apoptosis places pressure on stem cell populations to fill these voids, thus aging the stem cell population. Indeed the use of senolytic drugs in animal models restores tissue function through the clearance of

senescent cells, thus improving physical function in both young and old animals and providing evidence for the causal relationship between senescent cells and aging-related disease.[38]

Individuals under chronic psychological stress have shorter telomeres on average than individuals that are not stressed. Psychological stress may therefore be pushing cells toward either senescence or apoptosis faster than they may otherwise reach these states. Critically short telomeres have received much attention as a trigger for DNA damage responses and ensuing senescence or apoptosis. Here, we presented an additional role for telomeres as genome regulators. Changes in gene expression due to progressively shortening telomeres may drive an association between psychological stress and accelerated aging. Investigations into telomeres as genome regulators and the impact of psychological stress on telomere dynamics should focus on (1) prospective longitudinal studies of psychological stress exposure and telomere length across developmental time frames, (2) validation of observed gene expression changes with progressive telomere shortening due to psychological stress in vivo, and (3) elucidating the functional significance of these gene expression changes for cells and tissues. Future research in this direction hinges on overcoming methodological barriers in the field, notably the granularity with which we can measure individual telomere length in vivo. Recent work on the role of telomeres in modifying the cellular response to changes in the state of the cell highlights the critical need for high-throughput methods of measuring telomere–genome interactions at the level of individual telomeres. These measurements should be undertaken in tandem with other factors that may influence telomeres as genome regulators (e.g., oxidative stress, inflammatory cytokines, epigenetics, and nuclear concentrations and localizations of TERRA and shelterin proteins). Understanding the complex dynamics, linking telomeres as genome regulators to psychological stress has important implications for basic understanding of cellular processes and for the potential development of novel interventions and treatments to mitigate the impacts of stress on health.

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